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EXAMINER	
HADDAD, MAHER M	

ART UNIT	PAPER NUMBER
1644	

DATE MAILED: 11/30/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/802,644	MARTIN ET AL.	
	Examiner	Art Unit	
	Maher M. Haddad	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 September 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-4,8-14,20-27,31-34,37-42 and 47-51* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4,8-14,20-27,31-34,37-42 and 47-51* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *7/17/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. In view of the amended claims submitted on 3/17/04, the previous Non-Final rejection mailed on 10/21/04 is hereby vacated. The new Non-Final is set forth below. Examiner apologized for any inconveniences.

2. Claims 1-4, 8-14, 20-27, 31-34, 37-42 and 47-51 are pending.

3. A clear and obvious typographical error occurred in the restriction wherein claim 47 which reads on a method of reducing or inhibiting inflammation in a subject was not included a linking claim of Group I. Claim 47 will be examined along with elected group I.

4. Applicant's election with traverse of Group I, claims 1-4, 8-16, 20-27, 31-34, 37-42 and 47-51 (now 1-4, 8-14, 20-27, 31-34, 37-42 and 47-51) drawn to a method of regulating an inflammation or cellular secretory process (granule release) in a subject comprising administering a composition comprising a MANS peptide or an active fragment thereof wherein inflammation is respiratory diseases filed on 9/27/04 and the species election of COPD on 9/30/04, is acknowledged.

Applicant's traversal is on the grounds that Groups I-V are all classified within the same class and subclass and which all recite the same compositions and do not recite the "structurally distinct products" or "methods of using comprising distinct method steps". Applicant submits that cystic fibrosis should be within Group I as it is a respiratory disease. Applicant submits that the restriction is improper as the claims can be examined currently without "serious burden". This is not found persuasive because while the inventions of Groups I-IV are classified within the same class and subclass and recite the same compositions and methods of use comprising the same method of use, the different diseases recited in said Groups I-IV are distinct because the pathological conditions differ in etiologies and therapeutic endpoints; thus each condition represents patentably distinct subject matter. Further, if applicant wishes to submit that these inventions are obvious variants or clearly admit on the record that this is the case. In either instance, if the examiner finds one of the inventions unpatentable over the prior art, the evidence or admission may be used in a rejection under 35 U.S.C. § 103 of the other invention. Therefore the methods of regulating an inflammation of cellular secretory process of different diseases are distinct and independent, and searches of all groups would place an undue burden upon the examiner due to the distinct and divergent subject matter of each Group. Further, a prior art search also requires a literature search. It is an undue burden for the examiner to search more than one invention

While the specification on page 1 under 8¶ discloses that cystic fibrosis is a genetic disease, however, based on Applicant assertion that cystic fibrosis is a respiratory disease, then the Groups V is withdrawn from the Grouping in previous restriction requirement and the cystic fibrosis would be placed as a species of elected Group I, since Applicant elected COPD as a species of Group I then cystic fibrosis is withdrawn from further consideration as non-elected species.

The requirement is still deemed proper and is therefore made FINAL.

5. Claims 1-4, 8-14, 20-27, 31-34, 37-42 and 47-51 are under examination as they read on a method of regulating an inflammation or cellular secretory process (granule release) in a subject comprising administering a composition comprising a MANS peptide or an active fragment thereof wherein inflammation is respiratory diseases and COPD as the species.

6. Applicant's IDS, filed 3/17/04, is acknowledged, however, the International Search Report was crossed out but the references listed thereon had been considered.

7. The oath or declaration is defective. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. See MPEP §§ 602.01 and 602.02.

The oath or declaration is defective because inventor Yuehua Li Residence and P.O Address have been altered without being initialed and dated.

8. Claim 1 is objected to because of the following informalities: claim 1, line 4 is missing the alternative operator "or" after SEQ ID NO: 1. Correction is required.

9. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

10. Claims 2, 13, 26, 33 and 48 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a New Matter rejection.

The phrase "retains its ability to inhibit and inflammatory mediator" claimed in claim 2, 13, 26, 33 and 48 represent a departure from the specification and the claims as originally filed.

Applicant's amendment filed 3/17/04 does not point to the specification for support for the newly added limitations "retains its ability to inhibit and inflammatory mediator" as claimed in claims 2, 13, 26, 33 and 48. However, the specification does not provide a clear support for such limitation. The instant claims now recite a limitation, which was not clearly disclosed in the specification and recited in the claims as originally filed.

11. Claims 1-4, 8-14, 20-27, 31-34, 37-42 and 47-51 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The specification does not reasonably provide **enablement** for a method of inhibiting any "inflammatory mediator"/ "cellular secretory process" in a subject comprising: administering a composition comprising a MANS peptide consisting of an amino acid sequence of SEQ ID NO:1 or active fragment thereof in claim 1, that inhibits a cellular secretory process in a subject in claim 12, wherein said active fragment of the MANS peptide comprises at least six amino acids and retains its ability to inhibit an "inflammatory mediator" in claims 2 and 13, wherein said inflammatory mediator in an inflammation is caused by respiratory diseases in claims 3, wherein the respiratory diseases is COPD in claims 4; or a method of reducing "an inflammatory mediator" in a subject comprising administering any "compound" that inhibits the MARCS-related release of inflammatory mediators, whereby mucus secretion/inflammation in the subject is reduced compared to that which would occur in the absence of said treatment in claims 24 and 31, wherein the said compound is any "active fragment of a MARCKS protein" in claim 25 and 32, wherein said active fragment is at least six amino acids in length and retains its ability to inhibit an inflammatory mediator in claim 26 and 33, wherein said compound is a MANS peptide consisting of SEQ ID NO: 1 or any active fragment thereof in claims 27 and 34; or a method of "regulating" mucin granule release/excytotic secretion of airway mucin granules in a subject comprising administering any "compound" that regulates/inhibits mucin granule release, whereby mucin granules are reduced as compared to that which would occur in the absence of said mucin granules in claims 37 and 40, wherein said compound is an active fragment of any "MARCKS protein" in claims 38 and 41, wherein said compound is any "MANS peptide" in claims 39 and 42; or a method of reducing or inhibiting "an inflammatory mediator" in a subject comprising administering a therapeutically effective amount of a MANS peptide consisting of an amino acid sequence of SEQ ID NO: 1 or an active fragment thereof effective to reduce/inhibit an inflammatory mediator in a subject in claim 47, wherein said active fragment is at least six amino acids in length and retains its ability to inhibit an inflammatory mediator in claim 48, wherein said inflammatory mediators are produced by neutrophils in claim 49, the method further comprising a second molecule of any "antibiotic", any "antiviral compound" any "antiparasitic compound" any "anti-inflammatory compound" and any "immunosuppressant" in claim 51 . The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and or use the invention commensurate in scope with this claim.

The specification disclosure does not enable one skilled in the art to practice the invention without an undue amount of experimentation.

The specification does not provide a sufficient enabling description of the claimed invention. The specification discloses only a single MANS peptide of sequence (SEQ ID NO:1) with a disclosed activity of blocking mucin secretion through PKC/PKG dependent signaling in NHBE cells (e.g., page 16, 65¶). The instant claims encompass in their breadth *any* MANS peptide

fragment, any compound that "inhibits the MARCKS-related release of inflammatory mediators" or "regulates mucin granule release; or *any* inflammatory mediator, any antibibotic, any antiviral compound, any antiparasitc compound any anti-inflammatory compound any immunosuppressant, or any inflammation, any cellular secretory process including those that comprise "mucin granule release".

Besides SEQ ID NO: 1, there does not appear to be sufficient guidance in the specification as filed as to how the skilled artisan would make and use the various MARKS/ fragments, or any compound that inhibits MARCKS-related release of inflammatory mediators or regulates mucin granule release recited in the instant claims. A person of skill in the art would not know which MARCKS/MANS fragments or which compounds are essential, which peptides and compounds are non-essential, and what particular sequence lengths identify essential sequences "at least six amino acids in length". Besides, SEQ ID NO: 1, there is insufficient guidance to direct a person of skill in the art to select particular peptides or peptide lengths as essential for the suppression of mucin secretion dependent signaling. Without detailed direction as to which peptide sequences are essential to the function of MANS peptide of SEQ ID NO:1, a person of skill in the art would not be able to determine without undue experimentation which of the plethora of compounds that inhibits the MARCKS-related release of inflammatory mediators, or active fragments of a MARKS protein encompassed by the instant claims would share the ability to inhibit mucin secretion dependent signaling other than SEQ ID NO:1.

Beside SEQ ID NO:1, the specification is silent with respect to specifically which "compound", "MANS fragment" or "MARKS protein fragment" which are critical to the claimed inhibition of the release of mucin granule function such that one skilled in the art could predict which species would fall within the scope of the claims to be used in the method of inhibiting mucus secretion for the claimed diseases.

The instant claim language appears to encompass subsequences. For example, claims 1-2 reite fragments of SEQ ID NO: 1 and claim 25-26 recite an active fragment of MARCKS protein comprises at least six amino acids. Such a recitation does not require that the full length sequence set forth in SEQ ID NO:1; but rather encompasses any amino acid sequence comprising either the full length of SEQ ID NO:1or MARKS protein or *any subsequence thereof.* However, the specification does not appear to have provided sufficient guidance as to which subsequences of SEQ ID NO:1/MARKS would share the function of inhibiting mucin secretion dependent signaling. Neither does the specification appear to have provided any working examples of any functional subsequences. Thus it would require undue experimentation of the skilled artisan to determine which subsequences of SEQ ID NO:1 would have the function of the full length molecule.

Furthermore, claims 47-51 recite the reducing/inhibiting an inflammatory mediator, however there are no working examples in the specification to modulate any neutrophils, basophils, eosinophils, monocytes or leukocytes. There is no evidence of record that demonstrates that the MANS peptide would function to modulate those inflammatory mediators. The lack of any working examples is exacerbated because the invention is in a highly unpredictable art-

regulating the airway mucus hypersecretion-and while the level of skill of a practitioner in the art may be high, the state of the prior art is that it is in fact unknown and untested what are the underlying inflammatory mediators and the physiologic bases of the therapeutic effects of MANS peptide in the treatment of inflammation.

Also, at issue is whether or not the claimed MANS peptide of SEQ ID NO: 1 would function to regulate "respiratory disease" including "CODP". The specification discloses the inhibition of mucin secretion dependent signaling of PKC/PKG using MANS peptide of SEQ ID NO:1. The exemplification in the specification is drawn to the blocking of mucin secretion from NHBE cells, a human bronchial epithelial, using *in vitro* ELISA assays. While such *in vitro* assay may provide an indication that particular compounds/compositions are appropriate to target for *further experimental consideration*. Applicant's disclosure does not appear to have provided the skilled artisan with sufficient guidance and support as how to extrapolate data obtained from *in vitro* assay to the development of effective *in vivo* human therapeutic methods, commensurate in scope with the claimed invention.

The inhibition of mucin secretion of NHBE cells exposed to the MANS peptide of SEQ ID NO:1, is primarily an in vitro method to assess the suppression of mucin secretion using MANS peptide of SEQ ID NO:1, which is evaluated for use in respiratory diseases therapy. It is unclear which patients would be candidates for in vivo treatment with MANS peptide and when a patient would be given antibiotics, antiviral compounds, antiparasitic compounds, anti-inflammatory compounds or immunosuppressants. In addition, although SEQ ID NO:1 was to block mucin hypersecretion induced by PMA+8-Br-cGMP or UTP of the NHBE cells, it is unclear if these assay results are predictive of a method of inhibiting an inflammation/cellular secretory process/exocytoic secretion of airway mucin granules/mucus secretion in a subject comprising administering MANS peptide consisting of SEQ ID NO:1.

In re Fisher, 166 USPQ 18 indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute. Since no animals were used as model system to regulate/reduce/inhibit a COPD disease or to regulate cellular secretory process. It is not clear that reliance on the *in vitro* data of NHBE cells blocking of mucin secretion accurately reflects the relative mammal efficacy of the claimed therapeutic strategy. The specification does not adequately teach how to effectively regulate a COPD disease or cellular secretory process or reach any therapeutic endpoint in mammals by administrating the therapeutic composition of MANS peptide. The specification does not teach how to extrapolate data obtained from an in vitro assay studies to the development of effective in vivo mammalian therapeutic treatment, commensurate in scope with the claimed invention. Therefore, it is not clear that the skilled artisan could predict the efficacy of the therapeutic package exemplified in the specification.

In addition, for one to successfully use SEQ ID NO:1 in vivo, which is suggested to work by blocking PKC/PKG activation (see specification paragraph 65), it is essential to understand if those molecules targeted participant in those conditions in vivo, what blocking intervention is most appropriate and the general criteria which will define quantitative endpoints for accessing efficacy (see Ward et al., page 166, section on "Strategies..", in particular, IDS Ref. No. 3).

While the specification relies upon inhibiting mucin secretion with SEQ ID NO:1 as an assay for MANS peptide activity (see paragraph 71 of the instant specification), no such efficacy is disclosed. Barnes PJ. (Novartis Found Symp. 248:237-49; discussion 249-53, 277-82, 2002, IDS Ref. No. 2) discusses the current and future therapies for airway mucus hypersecretion. Barnes teaches that several novel targets involved in mucus hypersecretion have recently been identified, including epidermal growth factor receptors, MARCKs, Ca2+-activated Cl- channels and mitogen-activated protein kinases. However, the clinical benefits from inhibiting mucus hypersecretion are still not certain, casting some doubts on this therapeutic approach (see abstract page 237 in particular).

It has been held by the Court that "First, although appellants' specification describes certain in vitro experiments, there is no correlation on this record between in vitro experiments and a practical utility in currently available form for humans or animals. It is not enough to rely on in vitro studies where, as here, a person having ordinary skill in the art has no basis for perceiving those studies as constituting recognized screening procedures with clear relevance to utility in humans or animals" (emphasis added). Ex parte Maas, 9 USPQ2d 1746.

Further, if the use disclosed is of such nature that the art is unaware of successful treatments with chemically analogous compounds, a more complete statement of how to use must be supplied"Substantiating evidence may be in the form of animal tests which constitute recognized screening procedures with clear relevance to utility in humans. See Ex parte Krepelka, 231 USPQ 746 (Board of Patent Appeals and Interferences 1986) and cases cited therein." Ex parte Maas, 9 USPQ2d 1746

In view of the absence of a specific and detailed description in Applicant's specification of how to effectively use the methods as claimed, and absence of working examples providing evidence which is reasonably predictive that the claimed methods are effective for in vivo use, and the lack of predictability in the art at the time the invention was made, an undue amount of experimentation would be required to practice the claimed methods with a reasonable expectation of success.

12. Claims 1-4, 8-14, 20-27, 31-34, 37-42 and 47-51 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Applicant is in possession of MANS peptide molecule of SEQ ID NO: 1 for in vitro use to block mucin secretion.

Applicant is not in possession of a method of inhibiting any "inflammatory mediator"/ "cellular secretory process" in a subject comprising: administering a composition comprising a MANS peptide consisting of an amino acid sequence of SEQ ID NO:1 or active fragment thereof in claim 1, that inhibits a cellular secretory process in a subject in claim 12, wherein said active

fragment of the MANS peptide comprises at least six amino acids and retains its ability to inhibit an "inflammatory mediator" in claims 2 and 13, wherein said inflammatory mediator in an inflammation is caused by respiratory diseases in claims 3, wherein the respiratory diseases is COPD in claims 4; or a method of reducing "an inflammatory mediator" in a subject comprising administering any "compound" that inhibits the MARCS-related release of inflammatory mediators, whereby mucus secretion/inflammation in the subject is reduced compared to that which would occur in the absence of said treatment in claims 24 and 31, wherein the said compound is any "active fragment of a MARCKS protein" in claim 25 and 32, wherein said active fragment is at least six amino acids in length and retains its ability to inhibit an inflammatory mediator in claim 26 and 33, wherein said compound is a MANS peptide consisting of SEQ ID NO: 1 or any active fragment thereof in claims 27 and 34; or a method of "regulating" mucin granule release/excytotic secretion of airway mucin granules in a subject comprising administering any "compound" that regulates/inhibits mucin granule release, whereby mucin granules are reduced as compared to that which would occur in the absence of said mucin granules in claims 37 and 40, wherein said compound is an active fragment of any "MARCKS protein" in claims 38 and 41, wherein said compound is any "MANS peptide" in claims 39 and 42; or a method of reducing or inhibiting "an inflammatory mediator" in a subject comprising administering a therapeutically effective amount of a MANS peptide consisting of an amino acid sequence of SEQ ID NO: 1 or an active fragment thereof effective to reduce/inhibit an inflammatory mediator in a subject in claim 47, wherein said active fragment is at least six amino acids in length and retains its ability to inhibit an inflammatory mediator in claim 48, wherein said inflammatory mediators are produced by neutrophils in claim 49, the method further comprising a second molecule of any "antibiotic", any "antiviral compound" any "antiparasitic compound" any "anti-inflammatory compound" and any "immunosuppressant" in claim 51.

Neither the exemplary embodiments nor the specification's general method appears to describe structural features, in structural terms, that are common to the genus. That is, the specification provides neither a representative number of species (active fragment of a MARKS protein) to describe the claimed genus, nor does it provide a description of structural features that are common to species (active fragment of a MARKS protein). The specification provides no structural description of an active fragment of a MARKS protein other than SEQ ID NO:1; in essence, the specification simply directs those skilled in the art to go figure out for themselves what the claimed peptide/fragment looks like. The specification's disclosure is inadequate to describe the claimed genus of active fragment of a MARKS protein.

Applicant has disclosed only MANS peptide consisting of SEQ ID NO: 1; therefore, the skilled artisan cannot envision all the contemplated active MANS peptide fragment or compound possibilities recited in the instant claims. Consequently, conception cannot be achieved until a representative description of the structural and functional properties of the claimed invention has occurred, regardless of the complexity or simplicity of the method. Adequate written description requires more than a mere statement that it is part of the invention. See *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (CAFC1993). The Guidelines for the Examination of Patent Application Under the 35 U.S.C.112, ¶ 1"Written Description" Requirement make clear that the written

description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species disclosure of relevant, identifying characteristics, i.e., structure or other physical and or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the genus (Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 20001, see especially page 1106 3rd column).

Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the written description inquiry, whatever is now claimed." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116.). Consequently, Applicant was not in possession of the instant claimed invention. See University of California v. Eli Lilly and Co. 43 USPQ2d 1398.

Applicant is directed to the Revised Interim Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

13. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> *(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.*

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

14. Claims 1-4, 8-14, 20-27, 31-34, 37-42, 47-48 and 50 are rejected under 35 U.S.C. 103(a) as being unpatentable over Adler et al (CHEST. May, 2000, of record), as is evidenced by the specification on page 26, lines 11-15.

Adler et al teach that the mucin hypersecretion provoked by the pathophysiological relevant secretagogue, uridine triphosphate, or by a combination of PMA+ 8 bromo-cGMP, was inhibited in a concentration-depenent manner by a synthetic peptide with a identical to the myristic acid containing N-terminal region of MARCKS protein, the site of its attachment to granule membranes. Adler et al teach that the PKC inhibitor, calphostin C, the cGMP inhibitor, Rp-8-Br-PET-cGMP, or the phospatase inhibitor, okadaic acid, independently inhibited mucin secretion provoked by the mentioned secretagogues (see the entire document). Further, as is

evidenced by the specification on page 26, lines 11-15, that the MANS peptide consisted of sequence identical to the first 24 amino acids of MARCKS, i.e. the myristoylated N-terminal region that mediates MARCKS insertion into membranes (claimed SEQ ID NO:1). Further, Adler et al teach that hypersecreation of mucus contributes to air way inflammation and obstruction in COPD. Adler et al further teach that the MARCKS protein is a major cellular substrate for protein kinase C, is a central, convergent intracellular molecule controlling release of mucine granules by airway goblet cells.

The claimed invention differs from the reference teachings only by the recitation that the method of inhibiting an inflammatory mediator in a subject in claim 1, wherein the subject is a mammal in claim 8, wherein the mammal is selected from the group consisting of humans, canines, equines and felines in claim 9.

Given that hypersecreation of mucus contributes to air way inflammation and obstruction in COPD and that MARCKS protein is a major cellular substrate for protein kinase C, is a central, convergent intracellular molecule controlling release of mucine granules by airway goblet cells, it would have been obvious to one of ordinary skill in the art at the time the invention was made to consider practice the method taught by Adler et al in mammalian subject including humans.

One of ordinary skill in the art at the time the invention was made would have been motivated to do so because the inhibition of mucin secretion alleviate hypersecretion of mucus cause by airway inflammation taught by Adler et al and further, Adler et al suggest the in vivo treatment implicitly.

Claims 10-11, 22-23 and 50 are included because it would be conventional and within the preview of those skilled in the art to identify and determine the administering routs and formulation to regulate inflammation and mucin secretion in humans. Especially, since the condition is airway inflammation, pulmonary administration would be the target. Further, it has been held that where the general conditions of a claim are disclosed in the prior art, discovering the optimum or workable ranges involves only routine skill in the art. *In re Aller*, 220 F2d 454,456,105 USPQ 233; 235 (CCPA 1955). see MPEP § 2144.05 part II A.

From the reference teachings, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the reference, especially in the absence of evidence to the contrary.

15. Claim 51 is rejected under 35 U.S.C. 103(a) as being unpatentable over Adler et al (CHEST. May, 2000, of record), as is evidenced by the specification on page 26, lines 11-15, as applied to claims 1-4, 8-11, 12-16, 20-27, 31-34, 37-42, 47-48, 50 above, and further in view of U.S Patent No. 6,506,779 of record.

The teachings of Adler et al reference have been discussed, supra.

The claimed invention differs from the reference teachings only in that they do not teach the administration of a second molecule of an antibiotics or antiviral.

The '779 patent teaches a method of for treating inflammatory processes and diseases comprising administering an inhibitory compound which is used in combination with one or more antibiotic, and/or antiviral therapeutic agents. The `779 patent further teaches that such agents can be used when a multi-fold treatment of pain and inflammation is desired (see column 12, line 11-30).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to combined the MANS peptide or an active fragment thereof with the antibiotic or antiviral compound taught by the `779 patent, were known to alleviate inflammation, as taught by the '779 patent.

One of ordinary skill in the art at the time the invention was made would have been motivated to combine the antibiotic or antiviral compound taught by the `779 patent because the antibiotics are known to treat inflammation and said combination of additional antibiotics or antiviral would be considered obvious. "It is *prima facie* obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose. . . [T]he idea of combining them flows logically from their having been individually taught in the prior art." *In re Kerkhoven*, 626 F.2d 846, 850, 205USPQ 1069, 1072 (CCPA 1980) (see MPEP 2144.06).

16. No claim is allowed.

17. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Maher Haddad whose telephone number is (571) 272-0845. The examiner can normally be reached Monday through Friday from 7:30 am to 4:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (571) 272-0841. The fax number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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